## REMARKS

Reconsideration and allowance of pending claims 1-9 and 11-12 are respectfully requested.

The specification has been amended to include an abstract, which is based upon the subject matter of amended claims 1 and 9. No new matter has been introduced via this amendment to the specification.

Upon entry of this amendment, claims 1-9 and 11-12 will be pending in this application, claim 10 having been canceled without prejudice or disclaimer. New claims 11-12 have been added, and find support in the subject matter of canceled claim 10. Claim 9 has been amended to correct for grammatical insufficiencies according to U.S. patent practice, and to correct dependency. Claims 1 and 2 have been amended to more clearly recite the subject matter deemed the invention. Support for the amendments to the claims can be found throughout the application as filed. In particular, support for amended claims 1-2 can be found in the specification at page 1, lines 3-8, and page 3, lines 16-31. Applicants respectfully submit that no new matter has been introduced into the application via these amendments to the claims.

Claims 1-2 and 5-7 were rejected under 35 U.S.C. §102(b) as being anticipated by a 1995 Gene Therapy and Molecular Medicine abstract authored by Demoor et al. (hereinafter Demoor 1995). According to the Examiner, Demoor 1995 discloses a method of downregulating thymidylate synthase activity in human tumor cells by administration of antisense oligonucleotides to these cells. The Examiner also contends that the combination of thymidylate synthase antisense

oligonucleotide and chemotherapeutic drugs such as Tomudex and 5-fluorouracil. Applicants traverse this rejection for at least the following reasons.

Demoor 1995 discloses antisense oligonucleotides targeted to the translation start site (at the 5' end of TS mRNA) and the exon 1/exon 2 boundary. Antisense oligodeoxynucleotides targeted to sequences at or near the translation start site at the 5' end of thymidylate synthase mRNA have no effect on cell replication, or serve to enhance tumor cell growth when administered alone.

By contrast, the claimed invention is an antisense oligonucleotide that hybridizes to the 3' end of a thymidylate synthase target nucleic acid sequence, which selectively inhibits thymidylate synthase production. Thus, the structural aspects of the claimed antisense oligonucleotides differ from the oligonucleotides disclosed in Demoor 1995 . Functionally, the inventive antisense oligonucleotides are cytostatic when individually administered to human tumor cells. Antisense oligonucleotides that hybridize to the 3' end of a target nucleic acid sequence in thymidylate synthase according to the invention also enhance the toxicity of anticancer drugs, such as Tomudex, toward cancer cells. Since the oligonucleotides disclosed in Demoor 1995 have no effect on cell replication, or serve to enhance tumor cell growth, the claimed oligonucleotides are functionally distinct from those of Demoor 1995. Accordingly, the oligonucleotides of Demoor 1995 fail to anticipate the claimed invention. Applicants respectfully submit that the Section 102-based rejection in view of Demoor 1995 should be withdrawn.

Claims 1-6 were rejected under 35 U.S.C. §102(b) as being anticipated a 1996 thesis authored by Ju[1] (hereinafter, Ju 1996). The Examiner asserts that Ju 1996 teaches the expression of an antisense vector comprising the antisense

[1] The reference is not Ju et al., as the cited reference is an individual's University thesis.

sequence of thymidylate synthase that is capable of increasing the sensitivity of cancer cells to fluoropyrimidine drugs. The Examiner states that the open nature of the claim language embraces the antisense vector of Ju 1996. Applicants traverse this rejection for at least the following reasons.

The Ju 1996 reference discloses antisense oligonucleotides targeted at the translation site at the 5' end of thymidylate synthase mRNA. Such oligonucleotides do not anticipate the claimed invention. Ju 1996 fails to teach the claimed antisense oligodeoxynucleotides targeted to the sequences of the 3' end of the thymidylate synthase mRNA. Therefore, the Section 102-based rejection over Ju 1996 should be withdrawn.

Claims 9-10 were rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to distinctly claim the subject matter deemed the invention. Claims 9 and 10 were rejected for lack of antecedent basis. Cancellation of claim 10 renders moot the rejection in view of this claim. Amended claim 9 depends from claim 5, thereby providing proper antecedence. Withdrawal of the Section 112(2)-based rejections is respectfully requested.

Claim 10 was rejected under 35 U.S.C. § 101 as being directed to nonstatutory subject matter that is unpatentable. Cancellation of claim 10 renders this rejection moot.

Claims 1-2, 5 and 8 were rejected under 35 U.S.C. § 112, first paragraph, for failing to be supported by an adequate written description in the specification. Claims 8-10 were 35 U.S.C. § 112, first paragraph, for lack of enablement. Applicants traverse these Section 112, first paragraph-based rejections for at least the following reasons.

Applicants note that the specification clearly discloses throughout its entirety oligonucleotides that target specific loci in thymidylate synthase. One of ordinary skill in the art would be able to devise other antisense oligonucleotides that target the same loci using routine experimentation. Similarly, using the human thymidylate synthase sequence, a skilled artisan would be able to identify corresponding loci in other mammalian genomes. The claims are adequately supported by the written description set forth in the specification.

Regarding the pharmaceutical composition of claim 8 and method of claim 9, Applicants submit that the antisense oligonucleotides embraced by the specification are both suitable and useful in regulating thymidylate synthase production in mammalain cells. The antisense oligonucleotides of the invention may be administered by injection, as set forth at page 9, lines 7-21.

The Examiner objected to the application for containing a Sequence Listing, but failing to submit a CRF version of the Sequence Listing together with the application. Applicants note that the Examiner stated in the Office Action that a CRF was submitted at the time of filing, but was not processable for the reasons set forth in an attached CRF Diskette Problem Report. Applicants never received such a report, and a telephone call to the Examiner failed to reveal the existence of said report.

In an effort to comply with 37 C.F.R. §1.821 *et seq.*, Applicants submit herewith a CRF and a substitute paper copy of the Sequence Listing contained in the application as filed. The two paper versions are substantively identical. Kindly replace the previously submitted paper copy of the Sequence Listing with the paper version submitted herewith. The contents of the newly submitted CRF version and newly submitted paper version of the Sequence Listing are the same, as noted in the

attached Statement of Support. No new matter will be introduced into the application via entry of the newly submitted CRF version and newly submitted paper version of the Sequence Listing.

In view of the foregoing amendments and remarks, Applicants respectfully submit that the application is in condition for allowance. Notification to that effect is earnestly solicited. Should questions related to patentability remain, the Examiner is invited to telephone the undersigned to discuss the same.

Respectfully Submitted,

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## APPENDIX

## MARK UP VERSION SHOWING CHANGES MADE

**IN THE SPECIFICATION:**

The specification has been amended to incorporate the ABSTRACT on the following page.

**IN THE CLAIMS:**

The claims have been amended as indicated.

1. (Amended) An antisense oligonucleotide that hybridizes [which hybridises] to a target 3' region of a mammalian thymidylate synthase nucleic acid sequence [in thymidylate synthase] and that [which] selectively inhibits thymidylate production in mammalian cells.

2. (Amended) An antisense oligonucleotide [which hybridises] that hybridizes to a target 3' region of a mammalian thymidylate synthase nucleic acid sequence [in thymidylate synthase] and [which] that selectively enhances thymidylate synthase production in mammalian cells.

9. (Amended) A method for the treatment of cancer or for providing an antiprolierative effect on cells comprising [which comprises] administering to a warm-blooded animal an effective amount of the combination product claimed in claim 5 [4].